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INVESTIGATIONS INTO THE GROWTH OF THE LYMPHOSARCOMATA IN DOGS.

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About eight years ago one of us showed that after a successful inoculation of a sarcoma of the thyroid of white rats, the peripheral parts of the transplanted cells remain alive and multiply rapidly by mitotic division. The new sarcomata arise in the host through a proliferation of the transplanted tissue. This fact was demonstrated by a methodical study of the transplanted pieces, excised at various periods (from a few hours to several weeks after transplantation).

Independently, Jensen showed the same process to take place after transplantation of adeno-carcinomata in mice. In regard to the tumors (lymphosarcomata or alveolar sarcomata) found in the genital region of dogs, opinions differ very much as to their mode of formation after transplantation.

Sticker[1] mentioned that the inoculated tumors originated through a multiplication of the transplanted cells. At early stages after transplantation he found the tumor cells alive, at first without stroma; later connective tissue and

[1] Zeit. f. Krebsforschung, 1906, vol. iv.

bloodvessels grew into the tumor nodule from the neighboring tissue of the host.

Bashford, Murray, and Cramer[1] disputed this fact, and stated that the formation of the growths resulted from an infection of the host, by an unknown microörganism. They believe that after transplantation a few tumor cells might remain alive for a few days, but that afterward the real, new tumor is produced through a proliferation of the fibroblasts in the host, and their transformation into tumor cells.

Beebe and Ewing[2] on the other hand, showed that after transplantation the peripheral tumor cells remained alive and definitely gave origin to the new growth. They did not see any picture indicating transformation of the cells of the host into tumor cells.

Notwithstanding the careful observations of these authors Wade,[3] the most recent investigator of this question, arrived at a different conclusion. He believes that after transplantation the tumors have a double origin arising from the transplanted tumor cells as well as through a transformation of the fibroblasts of the host. He, therefore, calls the tumor an infective sarcoma.

The problem of the origin of these tumors is a very important one, inasmuch as its recognition as a tumor, in the restricted sense in which this term is usually employed at the present time, presupposes that the tumor takes its origin from the original tumor cells and not through an infection of the neighboring cells of the host.

Whether such a conclusion is really justifiable we do not wish to discuss at the present time, but, however that may be, it is very necessary to determine which of the different views regarding the origin of the transplanted tumors is correct, especially as work on this tumor led to important discoveries, and as this tumor is still being used for further work. We therefore carried out several series of experiments with the aim of determining this question.

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[1] Scientific Report of the Cancer Research Fund, 1905, No. 2.

[2] Jour. Med. Research., 1906, vol. xv.

[3] Journ. Path. and Bact., vol. xii.

The first series of experiments was carried out on nine dogs.

A sarcomatous tumor was removed from a dog under aseptic precautions, the tumor divided into pieces, and these pieces inoculated into the nine dogs. These pieces of tumor tissue along with the surrounding host tissue were removed at various times after the transplantation and subjected to microscopic study.

1. The piece from the first dog was removed after twenty-four hours. Microscopically, the section showed in the periphery little groups of well-preserved living tumor cells. A connection with the surrounding tissue had not been established. At some places the tumor cells showed the presence of mitoses.

2. The piece from the second dog was removed after forty-two hours. Microscopically, it revealed little groups of tumor cells in the periphery, which showed the typical arrangement found in the original tumor. A few mitoses were present. There was a wall of connective tissue or fibrin separating the tumor cells from the outside tissue.

3. The piece from the third dog was removed after two days. Microscopically, it was found to be almost entirely necrotic. At a few places in the periphery there were some groups of living tumor cells. The typical arrangement was still preserved. The living tumor tissue was separated from the surrounding host tissue by a band of connective tissue, or fibrin.

4. The piece from the fourth dog was removed after three days. At a place in the periphery a few layers of living tumor cells could be seen. They were separated from the surrounding host tissue by a band of connective tissue or fibrin.

5. The piece was removed from Dog No. 5 after four days. Microscopically, there were considerable masses of well-preserved living tumor cells at places in the periphery. These cells extended toward the centre of the transplanted piece. Quite a number of mitoses were present. This tissue undoubtedly showed very active cell proliferation.

It was separated from the surrounding host tissue by fibrin or connective tissue. No proliferation of the surrounding host tissue could be seen.

6. The piece was removed from Dog No. 6 after five days. On one side of the periphery living proliferating tumor cells with many mitoses could be seen. At places around the periphery of the tumor there was connective tissue growing into the tumor from the host. At some places we found an alveolar arrangement of the tumor cells. At places there were many polynuclear leukocytes intermixed with the growing cells. The centre of the tumor was necrotic. There was absolutely no indication that the connective tissue of the host gave rise to the tumor cells. At one place there was a group of proliferated tumor cells which had no connection with the tissue of the host, being separated from the latter by layers of necrotic tissue and blood.

7. The piece was removed from Dog No. 7 after six days. All of the tumor tissue was necrotic. In the periphery, resting on the connective tissue reticulum, there were in places a few living cells which were perhaps tumor cells, but this was not at all certain. At many places between the necrotic tissue and the surrounding tissue there were many polynuclear leukocytes present, probably indicating bacterial infection.

8. The piece was removed from Dog No. 8 after eleven days. No necrotic material was visible; everywhere living tumor tissue was present. The tumor cells rested on a connective tissue reticulum leaving the centres of the reticulum meshes vacant. At some places, however, these meshes were filled with tumor cells, giving a solid appearance to the tumor structure. In such regions a few mitoses could be seen.

9. The piece was removed from Dog No. 9 after eleven days. The greater part of the centre was necrotic. In the periphery small masses of living tumor cells could be found. Between the latter and the necrotic area there was some dense connective tissue, and between this connective tissue and the necrotic area larger cells of an epithe-

lioid character were penetrating into the necrotic areas. These were possibly tumor cells. The leukocytic origin of these cells, however, cannot be excluded with certainty. Mitoses were present.

In the following series of experiments the greater portion of a sarcoma was excised from a dog under aseptic precautions and divided into a number of small pieces. These pieces were inoculated into six dogs, each dog was inoculated in four different places, with two pieces of tumor in each place. At various times after this operation the transplanted tissue was removed and subjected to microscopic study.

After six days a piece of the transplanted tissue was removed from Dogs Nos. 1, 2, 3, 4, 5, and 6.

Dog No. 1. Almost the whole piece was necrotic. In the periphery we found a small zone of living tumor cells. Mitoses were present. At places the periphery was necrotic. In the denser connective tissue of the periphery there were occasionally some small collections of cells which might have or might not have been tumor cells. Here again we found tumor cells which rested on the connective tissue reticulum, no cells being present in the centres of the meshes. In some places at the periphery we found collections of polynuclear leukocytes.

Dog No. 2. In this piece much more well-preserved tumor tissue was seen in the periphery. It surrounded an area of necrotic tumor tissue, in the centre of which a cavity had formed. The zone of tumor tissue in parts adjoined fat tissue, into which it penetrated, surrounding some of the fat cells. At other places it was bordered by edematous connective tissue, and here the demarcation was sharp. In the periphery numerous collections of polynuclear leukocytes were found. At some places the tumor adjoined striated muscle, between the fibers of which the tumor cells often penetrated. There was no indication that the tumor tissue might originate through proliferation of the connective tissue of the host, although at some places no sharp demarcation between the tissues existed. The tumor cells here and there penetrated the connective tissue. There were no

mitoses. The living tumor tissue seemed to have penetrated into the necrotic tissue and here the cells often assumed a spindle shape. There was no marked difference between the way in which the tumor tissue penetrated into the surrounding connective tissue, and the way in which it penetrated into the necrotic tissue. In the outer zone of the necrotic area large phagocytes were seen taking up the degenerated material.

Dog No. 3. The zone of living tumor tissue in this case was not quite so extensive as in Dog No. 2. Near the necrotic area large phagocytes were seen taking up the degenerated tumor cells. The tumor tissue at places penetrated the surrounding fat and included some of the fat cells. Quite a number of mitoses were seen. At places the tumor tissue penetrated through the fat tissue up to a dense fibrous band, and even penetrated this slightly. There was absolutely no sign that the tumor tissue originated from proliferation of the surrounding host tissues.

Dog No. 4. At several places there were some necrotic areas. Otherwise, the whole piece consisted of living tumor tissue.

Dog No. 5. A great part of this piece was necrotic, but in the periphery there were small areas of living tumor tissue, the cells of which rested on the reticulum and did not fill up the meshes, except in a few places. In the surrounding fat there were some cells which may or may not have been tumor cells. At some places there were certainly some tumor cells penetrating the fat.

Dog No. 6. In the centre of this piece there was an area of necrosis. In the periphery was found a large zone of tumor tissue. Its structure was loose, the cells resting on the reticulum and not filling the meshes. The tumor tissue penetrated into the necrotic area and here spindle-shaped cells were often found. Mitoses were present. The tumor penetrated the surrounding connective tissue. There was no sign that the connective tissue of the host became transformed into tumor tissue.

After fourteen days transplanted pieces were removed

from Dogs Nos. 1, 2, and 3. At this date no tumors were palpable in Dogs Nos. 4, 5, and 6.

Dog No. 1. Almost the whole piece consisted of well-preserved living tumor tissue. The tumor was composed of small nodules, the centres of some of which contained necrotic areas. This necrotic material was penetrated at places and replaced by living tumor tissue. Quite a number of mitoses were present. In many places we found large collections of small mononuclear round cells. In this case also the tumor penetrated into surrounding connective tissue. Again we found the tumor in many places bordered by a thick wall of dense connective tissue. The demarcation was very sharp. There was no proliferation of the cells of the connective tissue capsule on the side toward the tumor, but on the other side, toward the surrounding tissue, there were some mitoses present and cells proliferating into the surrounding fat. In the capsule the lymph vessels were filled with small round cells (lymphocytes). At places the tumor penetrated into the surrounding fat tissue. The tumor had a distinct infiltrating growth progressing into the connective tissue and separating it into strands.

Dog No. 2. No necrosis was found in this piece. The tumor tissue consisted of solid cell masses without cavities. Many mitoses were found, and many capillaries were surrounded by masses of round cells, which were distinct from the tumor cells. On one side, the tumor was surrounded by a thick wall of dense connective tissue, which showed no sign of any proliferation. At places the tumor cells penetrated into this capsule and separated the different lamellæ of connective tissue. There was no doubt that in this case the tumor growth took place entirely from its own tissue and received no additions from proliferation of the connective tissue. A small vessel was entirely filled with round cells (lymphocytes).

(The piece removed from Dog No. 3 was lost.)

After twenty-three days Dog No. 2 died, and at this time no tumors were palpable.

After forty-one days, in Dog No. 1 two tumors of about

two inches in diameter; in Dog No. 3, one tumor of one inch in diameter; in Dog No. 4, two tumors of one inch and one of two inches in diameter; in Dog No. 5, one of three inches and one of two inches in diameter; and in Dog No. 6, one of one inch and one of one-half inch in diameter were present. The dogs used for the second series of experiments were therefore not immune to tumor growth.

In a third series of experiments a sarcomatous tumor was removed from a dog, under aseptic precautions, divided into small pieces, and three pieces transplanted into the same dog from which the tumor had been excised (Dog No. 1); three into each of two previously inoculated dogs (Dogs Nos. 2 and 3); three into a dog with tumors retrogressing (Dog No. 4); three into three new dogs (Dogs Nos. 5, 6, and 7); and three into a dog (Dog No. 8) in which tumors were growing.

After seven days transplanted pieces were removed from Dogs Nos. 1, 2, 3, 4, 5, 6, 7, and 8. These pieces were mixed up during the embedding process and one piece was lost; hence we do not know from what dog any piece came, but we give the microscopic findings of the seven pieces examined, because these findings are of some value.

Piece *a*. Nearly all of this was necrotic. At a few places near the periphery were small areas of living tumor cells bounded on the outside by a wall of connective tissue. Some of these areas showed the presence of leukocytes. Around nearly the whole periphery there were numbers of leukocytes.

Piece *b*. This was nearly all necrotic. In the periphery there were some very small areas in which possibly tumor cells were situated in the midst of granulation tissue.

Piece *c*. This was mostly necrotic. A number of leukocytes were present at places in the periphery. At some places tumor cells surrounded fat cells in the areolar tissue. A number of mitoses were seen in the tumor cells around the periphery. Leukocytes were found here and there with the tumor cells.

Piece *d*. A great portion of this piece, namely in the centre, was necrotic. In the periphery at many places were living tumor cells, among which mitoses were seen. Bloodvessels connecting with the vessels of the surrounding tissue penetrating the living tumor tissue areas, usually in a radiating manner, were seen. Around a certain number of these vessels in the connective tissue surrounding the tumor, small round cells were present. These cells were, as a rule, smaller than tumor cells, but it was often difficult to differentiate them. At other parts in the periphery no tumor cells were seen. The bloodvessels in the periphery were to some extent newly formed. There were solid cell nests in the periphery without a central cavity. At places in the periphery there were masses of what appeared to be small, round cells (lymphocytes). At many places the demarcation between the tumor and connective tissue was quite sharp.

Piece *e*. The centre of this was necrotic. The periphery showed zones of living tumor tissue. At some places there were leukocytes among the peripheral tumor cells. Some mitoses were present. The tumor infiltrated the surrounding fat tissue, and at such places there was no sharp demarcation. The tumor cells in some places were scattered in the loose connective tissue surrounding the tumor. Phagocytes were present in the tumor tissue near the necrotic area, and penetrating into this area spindle cells were seen. Leukocytes were more numerous in the portion of the tumor tissue near the necrotic area.

Piece *f*. This piece showed scattered areas of necrosis, between which were areas of living tumor cells. Among these, round cells were present which were sometimes difficult to interpret. Around the necrotic areas phagocytes could be seen taking up the degenerated material. Strands of tumor cells were seen passing into the surrounding connective tissue, and in these places there was no sharp demarcation.

Piece *g*. Little necrosis was seen in this piece. At places polynuclear leukocytes were present. Around the periphery in the connective tissue masses of small cells,

some showing mitoses were seen. These surrounded the fat cells of the areolar tissue. At other places these cells were more scattered in a loose connective tissue, which was apparently edematous. Mitoses were present and also a number of polynuclear leukocytes. At places on the reticulum it is difficult to differentiate between the cells which form the reticulum and the cells which are in the meshes.

After fifteen days tumors were found to be growing in Dogs Nos. 2, 4, 5, and 6, and pieces of these tumors were removed at that time.

Dog No 2. The tumor and connective-tissue were sharply separated. There was no sign that the connective tissue gave rise to tumor formation. Some mitoses were present.

Dog No. 4. Necrotic tissue was present in the centre. A large white zone of living tumor tissue surrounded the central necrotic area. In the periphery toward the dense connective tissue capsule the tumor cells were small, in the centre they were larger. Near the interior of the mass there was a cavity and near the cavity were some small areas of necrotic tissue, around which were tumor cells large in size and containing vacuoles, indicating that these cells were phagocytic in character. Also at other places many cells took up the material. It is probable that the tumor cells themselves acted as phagocytes in this case. We, however, do not wish to exclude the possibility that immigrated cells of leukocytic origin also took up this function. Around the periphery of the piece there were masses of small, round cells in which some mitoses could be made out. In many places the tumor was sharply demarcated from the surrounding connective tissue, and there was no indication that the newgrowth came from this latter tissue. In that portion farthest removed from the newgrowth the connective tissue was edematous, and contained large round cells, spindle cells, and some large collections of small mononuclear cells.

Of interest was the finding in the centre, near the necrotic material, of homogenous masses which the tumor cells

penetrated and seemed to replace. It is very likely that these homogenous masses were produced through a partial dissolution of the necrotic material, and this probably represented one of the stages in the resorption of necrotic tumor tissue.

Dog No. 5. No sharp demarcation existed in this case between the tumor and the surrounding connective tissue. At some places along the margin of the tumor large cells were scattered in the surrounding connective tissue. Here and there masses of small round cells were seen in the periphery of the tumor. At other places the demarcation was quite sharp and the tumor cells sometimes penetrated between the lamellæ of the connective tissue capsule. During this process the tumor cells assumed a somewhat spindle shape. At some places the tumor was surrounded by loose connective tissue. Rows of tumor cells passed gradually into this loose connective tissue and here and there these tumors cells became isolated. The proliferation of spindle-shaped cells in the neighborhood of the tumor tissue was altogether too insignificant to account for the tumor formation. Similar appearances are seen in carcinomatous tumors, where on the same grounds we would have to assume a transformation of connective tissue cells into the carcinomatous cells. At places we saw a distinct swelling of the endothelial cells of the lymph vessels in the neighborhood of the tumor.

Dog No. 6. Nodules of tumor tissue were well preserved. The size of the tumor cells varied. Some of the nodules had large and some smaller cells, which probably depended upon variations in the pressure exerted by the cells. In the centre we found large masses of necrotic material. The latter was surrounded by many phagocytes, which often showed an arrangement similar to that of the tumor cells, filling out a fine reticulum of connective tissue. Here, again, these appearances suggested the conclusion that the tumor cells themselves may act as phagocytes removing the detritus of necrotic material.

In another series of experiments a portion of a large

sarcoma was removed from a dog, and three pieces were inoculated into each of four new dogs (1, 2, 3, and 4), two supposedly immune dogs (5 and 6), and one dog in which a tumor was already growing (7).

After four days, one of these transplanted masses was removed from Dogs 1, 2, 3, 4, and 7. Abscesses, but no tumor masses were found in Dog 5. No tumor masses could be determined in Dog 6.

Tumor from Dog No. 1: Microscopically, this mass was mostly necrotic. In the periphery around the blood-vessels proliferating cells were seen, but these were not typical tumor cells. A number of polynuclear leukocytes were present in the centre and periphery. The proliferating cells may have been either tumor cells or fibroblasts.

Tumor from Dog No. 2: Microscopically, this mass was mostly necrotic. In the periphery living tumor cells with mitoses were still preserved. These were arranged in nests. Among them we saw spindle-shaped cells, stellate and round cells, and polynuclear leukocytes. Quite outside of the above zone of tumor cells were to be seen vessels with proliferating cells around them, as in the mass from Dog No. 1. In some places we saw nests of tumor cells surrounded by fibrin, but no connective tissue. In other places connective tissue surrounded the nests. There was, if anything, more active proliferation of the connective tissue at a distance from the tumor tissue than in its immediate neighborhood. There were some irregular mitoses among the tumor cells. Quite a number of polynuclear leuko-cytes could be made out among the tumor cells, between them and the connective tissue, and also in the connective tissue. From examination of these sections there was no reason to believe that the connective tissue proliferation gave rise to the tumor.

Tumor from Dog No. 3: This mass showed a necrotic centre surrounded by living tumor tissue, but separated from it by a slight zone of connective tissue growing into the necrotic tumor tissue. Near the living tumor tissue, here and there, large cells (phagocytes) which took up the

necrotic tumor cells were present. In the ingrowing connective tissue polynuclear leukocytes were present.

Tumor from Dog No. 4: Microscopically, this mass showed a small zone of living tumor tissue at some parts of the periphery. The rest of it was necrotic. At some places in the periphery there were large numbers of polynuclear leukocytes. Connective tissue penetrated the necrotic areas in bands, and the living tumor cells were contained in these bands. Some mitoses were present.

Tumor from Dog No. 7: Microscopically, this tumor showed a necrotic centre surrounded by a fairly deep zone of living tumor tissue which had the same structure as the dead tissue, namely, groups or alveoli of tumor cells were surrounded by bands of connective tissue, which shows that the living tissue is not newly developed, but preserved tissue of the inoculated piece. At places only a dense capsule of fibrous connective tissue surrounded the necrotic tumor tissue. At other places the zone of living tumor tissue was bounded on the outside by a zone of necrotic connective tissue, or fibrin. At one place we found central necrotic tumor tissue surrounded by a zone of living tumor tissue, then a zone of hemorrhagic or necrotic tissue, and, on the outside a zone of proliferating connective tissue with polynuclear leukocytes and vessels. Hence, in this case, the living tumor tissue was entirely separated from the proliferating connective tissue by a zone of necrotic tissue.

After eleven days no tumors were found in Dogs Nos. 1 and 2. Tumors were removed from Dogs Nos. 3, 4, and 6, but tumors could not be determined in Dogs Nos. 5 and 7, but from these two dogs pieces of tissue were removed at the site of inoculation.

Tumor from Dog No. 3: Microscopically, this mass showed a great deal of living tumor tissue throughout. At some places this tumor included necrotic tumor tissue in which we could see red bodies, probably the remains of phagocytes. Polynuclear leukocytes were also present in the necrotic tissue. Around these areas of necrosis the

living tumor tissue was rather loose in structure, containing many edematous spaces and many polynuclear leukocytes. The tumor cells seemed to penetrate and replace the necrotic tissue. Here, again, we observed the tumor cells acting as phagocytes which took up the red, necrotic material and also living cells (round cells and polynuclears). The phagocytes showed an arrangement in rows similar to that of the tumor cells; they were continuous with the latter, and in no way could they be differentiated from each other. In the centre there was a cavity, probably resulting from autolysis of the tumor tissue. Bloodvessels radiated from the periphery to the central cavity. In the periphery the tumor cells were in dense formation, and there were still among them many cells (phagocytes) which contained foreign particles. In some places fresh hemorrhages existed between the tumor cells. The tumor was surrounded by dense connective tissue, its cells seemed to penetrate slightly into this capsule and, abundantly, into the surrounding fat tissue. In the capsule, at places, we saw masses of small round cells. Mitoses were present in the connective tissue surrounding the tumor.

Tumor from Dog No. 4: Microscopically, this mass showed a zone of living tumor tissue of considerable size. In the centre the greater part was necrotic and into this area penetrated rows of living tumor cells. In the living tumor zone the vessels, in places, were surrounded by masses of small round cells. Mitoses were present in the living tumor zone. In the surrounding capsule the tumor cells penetrated in rows between the connective tissue fibres. At some places in the periphery of the tumor masses of small round cells were present in much greater number than the tumor cells. We also found connective tissue containing tumor cells penetrating into necrotic areas. Phagocytes were present which took up the necrotic material. These phagocytes, after having taken up a number of necrotic cells, may themselves become necrotic and thus give rise to large necrotic masses in the shape of red balls. The tumor cells again appeared to be acting as phagocytes.

At places connective tissue strands without any accompanying tumor cells penetrated the necrotic material. At some points polynuclear leukocytes were seen.

Tissue from Dog No. 5: Microscopically, we found in this mass one small area of necrotic tissue surrounded by a large amount of dense connective tissue which, at places, penetrated the necrotic area. Numerous polynuclear cells were present in and around the borders of this necrotic tissue. No living tumor tissue could be made out.

Tumor from Dog No. 6: Microscopically, this mass showed a capsule of dense connective tissue inside of which was a wide zone of living tumor tissue containing eosinophiles, vessels surrounded by small round cells, and lymph vessels filled with the same. Some mitoses were present in the tumor zone. Lymph vessels filled with round cells were also present in the dense connective tissue. In the centre were necrotic areas. Around these regions were seen polynuclears and phagocytes, which latter seemed to be tumor cells lying on a reticulum. Tumor cells penetrated and gradually supplanted the necrotic tissue.

Tissue from Dog No. 7: Microscopically, the sections of this mass showed nothing but mammary gland tissue.

In another series of experiments an actively growing lymphosarcoma was removed from a dog, and pieces of this were placed in five other dogs in the following manner:

Small glass tubes one-half inch in length by one-quarter inch in cross-section were drawn out finely at one end so as to leave but a small aperture. Through the other end was inserted a piece of tumor tissue, and this end was then sealed up with paraffin having a very high melting point and a small hole punched through this paraffin so as to allow a free circulation of body juices through the capsule. Four of these capsules containing a piece of tumor were placed in each of five dogs; two under the skin; and two in the peritoneal cavity. At intervals of one week, two weeks, twenty-three days, thirty days, and forty-three days a subcutaneous and an intraperitoneal capsule were removed from one of the dogs. Their contents were placed in Zenker's

fluid, sectioned, and examined microscopically. None of the pieces examined showed a trace of tumor tissue. Sometimes the necrotic masses would show at the periphery numerous polynuclear leukocytes, and sometimes connective tissue was noted growing into the capsule from the outside. This series of experiments showed that tumor tissue, when transplanted in this manner, where it was subject to the action of the body juices, but not in direct contact with the tissues of the host, became necrotic and disappeared.

Conclusions. 1. Our investigations show, without any doubt, that the interpretation of Sticker, and of Beebe and Ewing, as to the origin of the sarcoma after transplantation of pieces of tumor, is correct. The examination of the pieces at different periods after transplantation proved that peripheral tumor cells remain alive and multiply very soon after transplantation. This mitotic cell multiplication continues and is the cause of the tumor formation. At the end of the first week an infiltrative growth of the tumor cells into the surrounding host tissue begins. At no time does the surrounding host tissue appear to participate actively in the tumor formation.

2. During the second and third weeks after transplantation a resorption of the necrotic centre of the transplanted piece takes place. Processes of liquefaction aid in the resorption and the necrotic material is supplanted by living tumor tissue, which grows actively into the central part of the transplanted piece. Similar processes have been described by Loeb after transplantation of the sarcoma in rats. Some facts suggest that the tumor cells themselves may act as phagocytes, taking up and removing necrotic debris.

3. Tumor material inserted in glass capsules before transplantation becomes necrotic and does not give rise to tumor formation notwithstanding the ready access of body fluids to the transplanted piece.